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WE'RE WAY PAST PEAS: USES OF GENETIC INFORMATION TO UNDERSTAND HUMAN HEALTH AND GUIDE HEALTH CARE DECISION MAKING

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Carolyn Martin, NN/LM Pacific Northwest Region






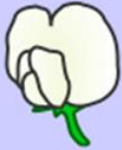
Topics for Today

- Basic principles of genetics
- Uses of genetics in health care; genetic testing
- BREAK
- NCBI MedGen portal; other clinical genetics resources.
- Answer practice questions using MedGen
- Genetic health literacy & genetic science literacy
- Genetic consumer health resources
- Direct-to-consumer testing
- Ethics and privacy
- Precision Medicine Initiative

Presentation slides are available at: <https://nnlm.gov/pnr/training/presentations>

Mendel Discovered Patterns of Inheritance by Studying Physical Traits

Before genes were discovered, Mendel realized that he could make mathematical predictions about the inheritance of physical traits – like flower color.

		 pollen ♂	
		B	b
 pistil ♀	B	 BB	 Bb
	b	 Bb	 bb

Mary-Claire King: Way Past Peas!



Mary-Claire King: Way Past Peas!

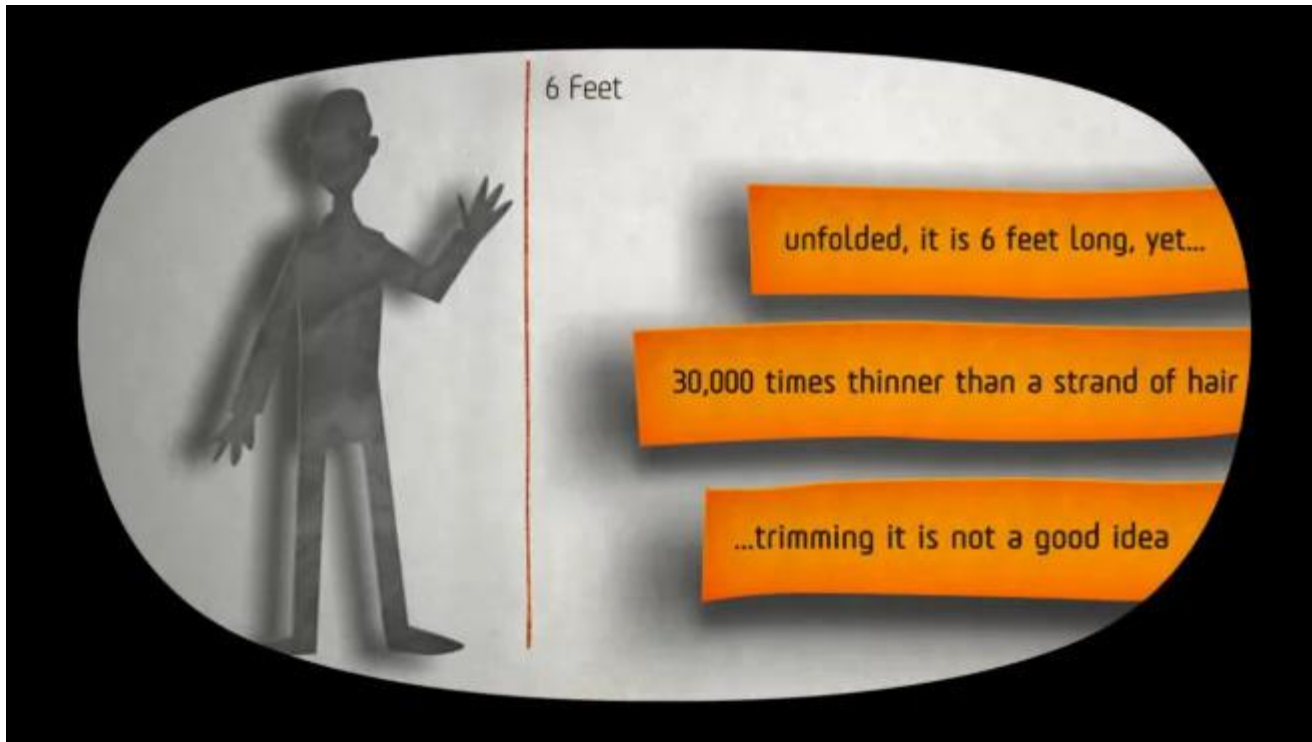
Transforming the Diagnosis and Prevention of Breast Cancer

- Some cases of breast cancer clustered in families; must be inherited.
- In 1990 demonstrated that a single gene, which she named BRCA1, was responsible for breast and ovarian cancer in many families.
- Studied how mutations in BRCA1 lead to breast cancer. (BRCA1 is a tumor suppressor gene.)
- Now recommends that all women should be offered genetic testing for BRCA1 and BRCA2 mutations at about age 30 as part of routine medical care. “About half of women who inherit mutations in BRCA1 or BRCA2 have no family history of breast or ovarian cancer and have no idea they are carrying cancer-causing mutations.”
- “Most of inherited breast and ovarian cancer can be prevented, if mutation carriers know who they are.”

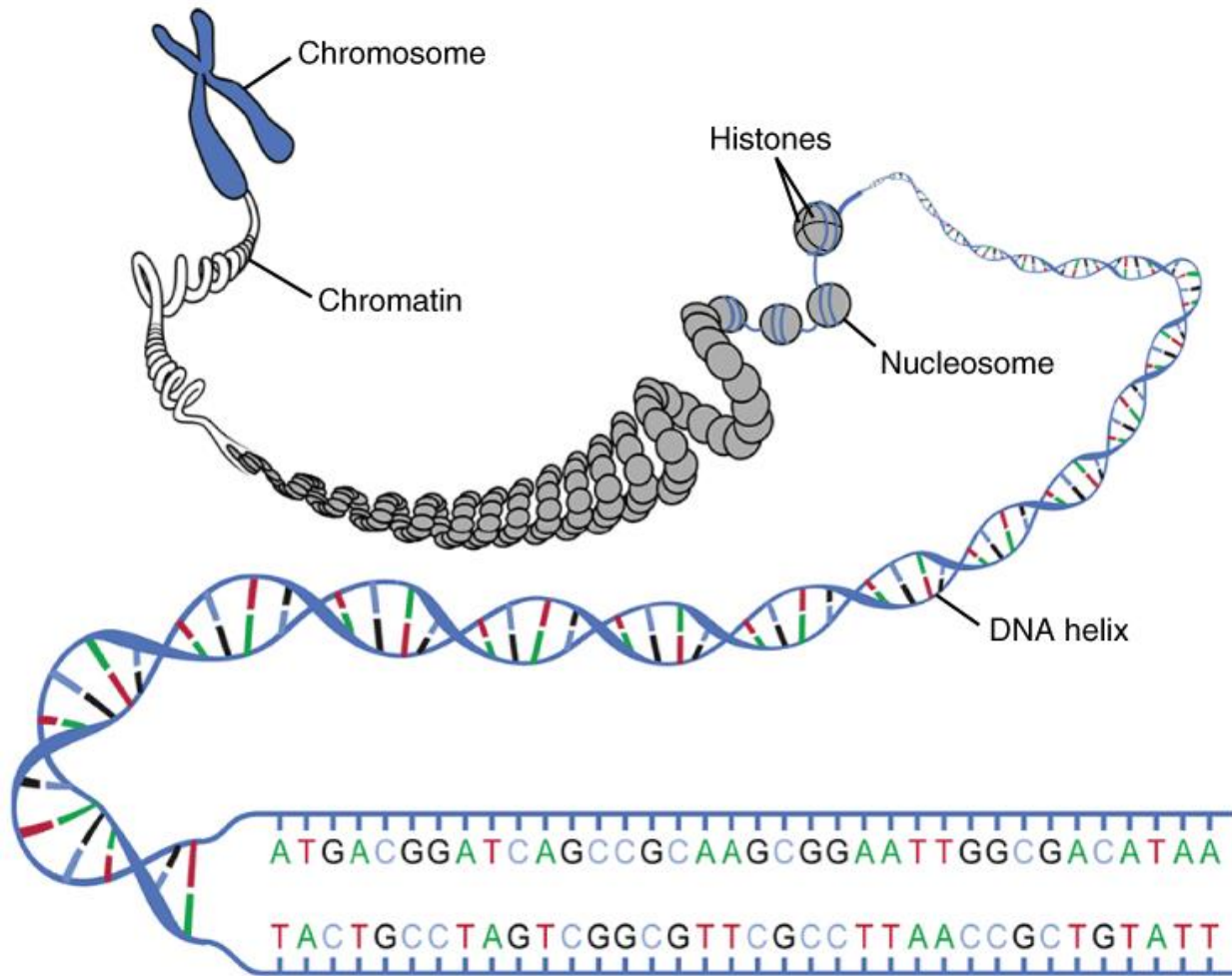
The Animated Genome

[Unlocking Life's Code video](https://unlockinglifescode.org/media/animations/659#660)

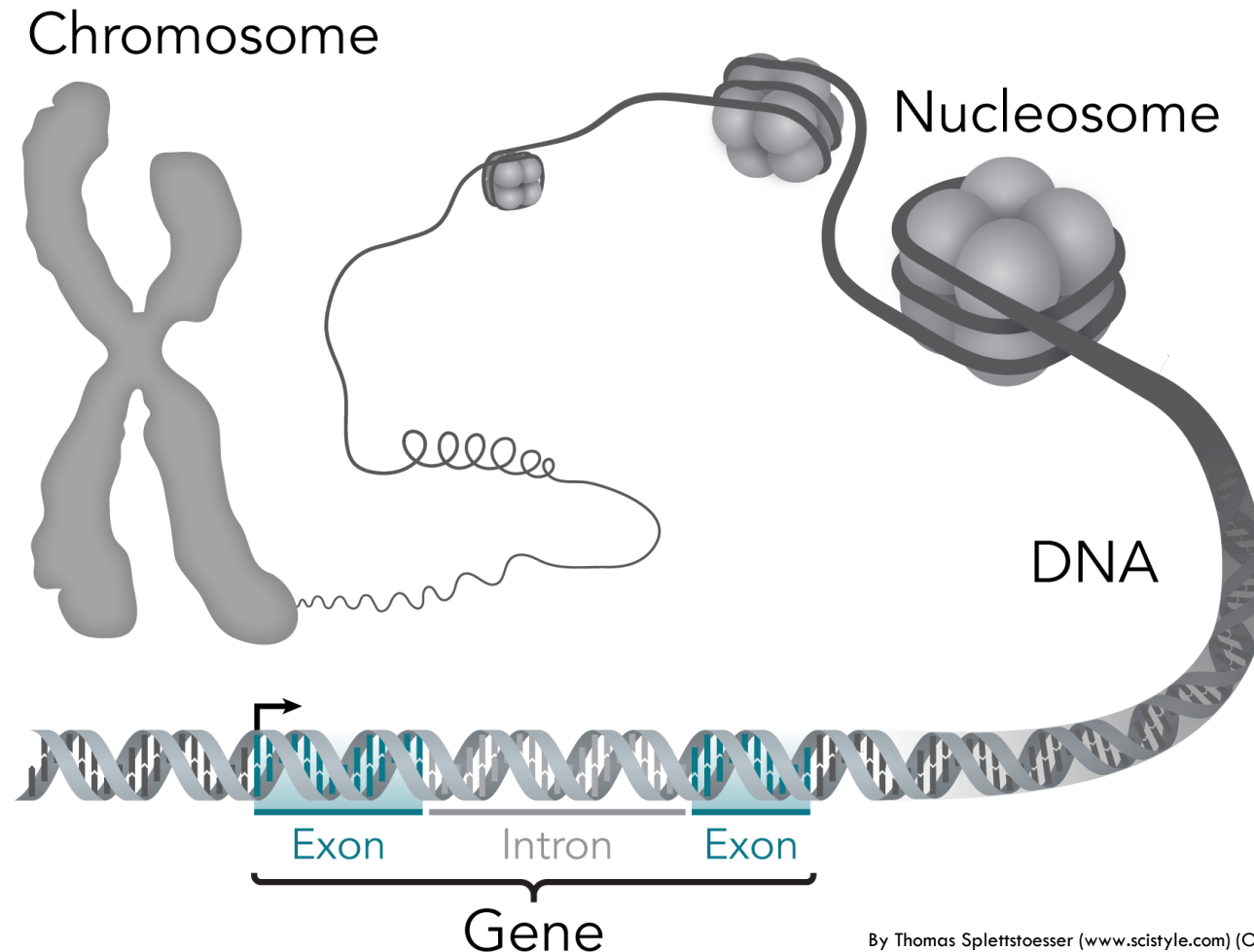
<https://unlockinglifescode.org/media/animations/659#660>



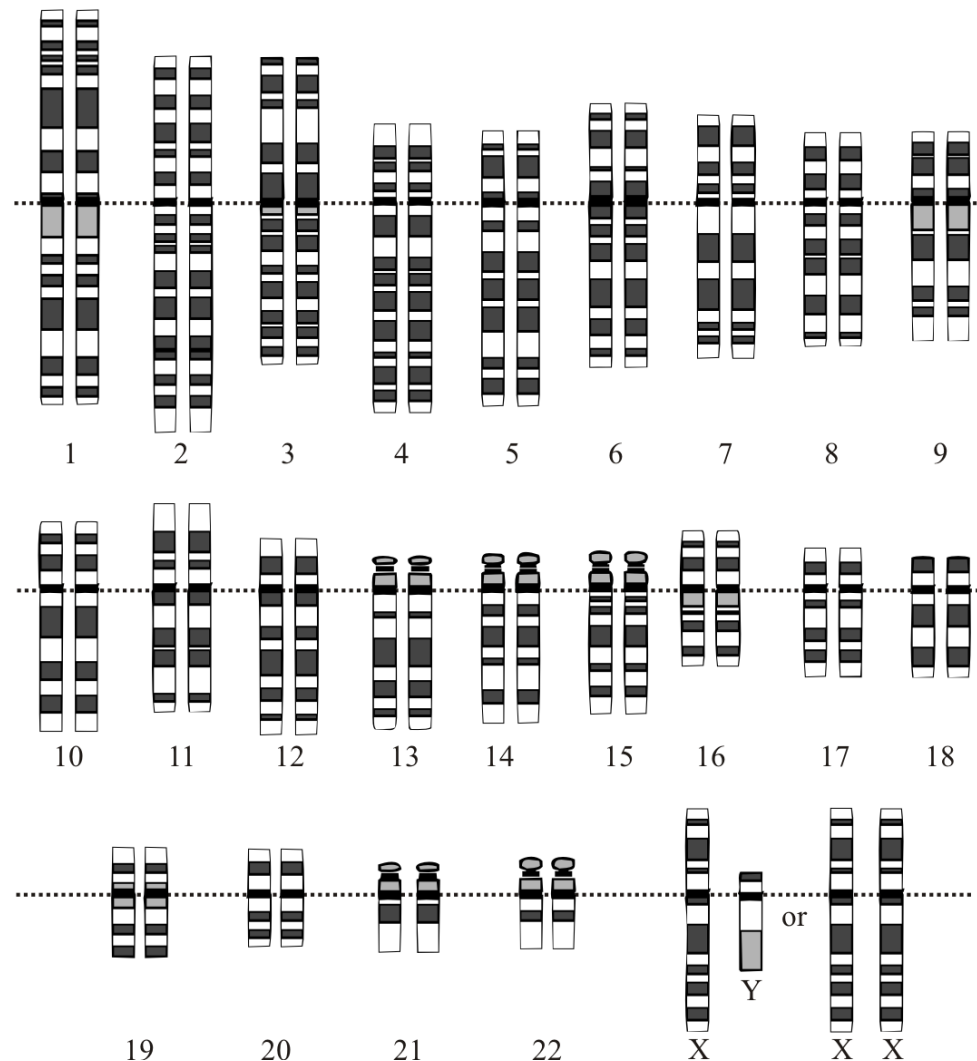
Chromosomes are made of DNA



Genes are discrete segments of DNA found on chromosomes



Humans Receive 23 Chromosomes from Each Parent; Each of Your Cells Contains These 46 Chromosomes*

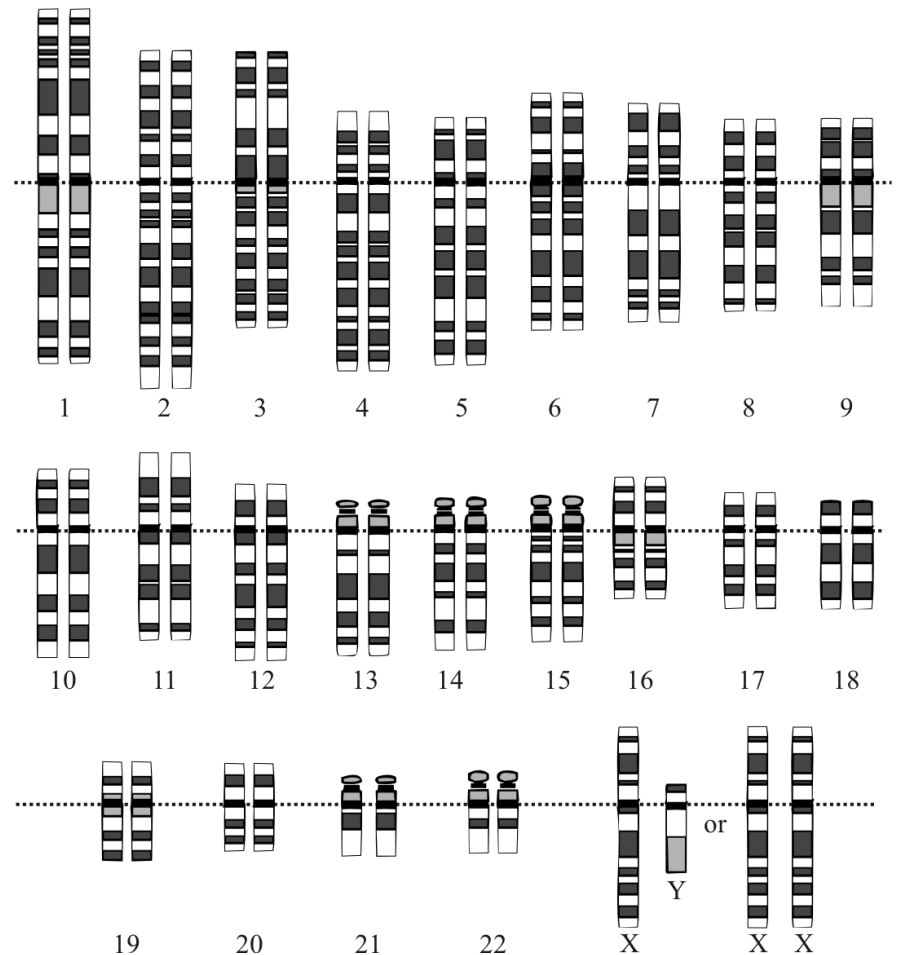


*Egg and sperm cells only contain one set of 23 chromosomes.

By Courtesy: National Human Genome Research Institute [Public domain], via Wikimedia Commons

This is Your Genome

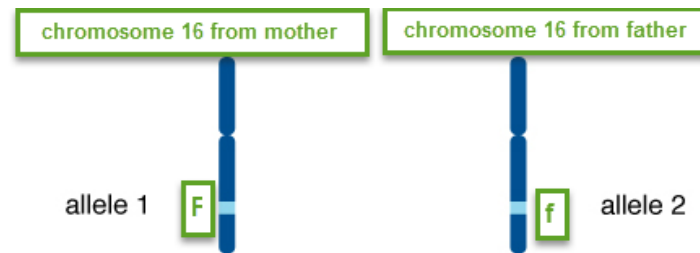
- The DNA that contains your 20,000+ genes.
- The DNA that regulates the expression of your genes.
- The DNA of unknown significance.



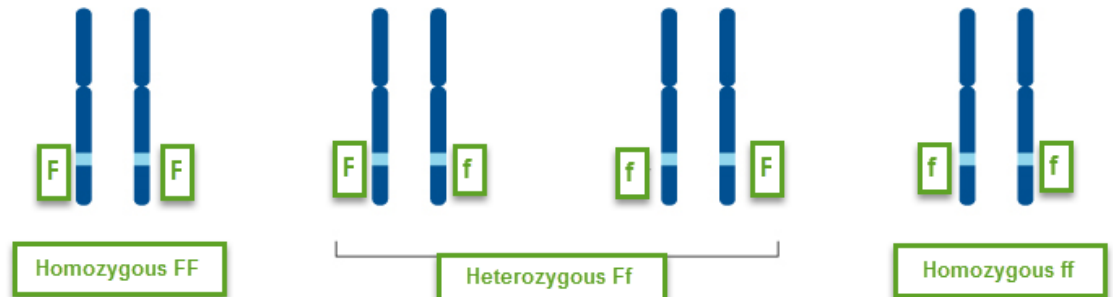
Each pair of chromosome has the same genes at the same locations, but possibly different alleles (versions).



“F” represents the freckle gene – MC1R on chromosome 16. Freckles are a dominant trait, so if you receive at least one copy of the F allele, you are likely to have freckles.



An allele is one of two or more versions/variants of a gene within a population.



Many Traits Are Multigenic – the Product of Multiple Genes

Eye color is determined by variation at several different genes and the interactions between them.

Brown Eyes



How does a gene affect a physical trait or process?

- Genes encode proteins.
- The DNA sequence dictates the amino acid sequence of the protein.
- Proteins do the work in your body.

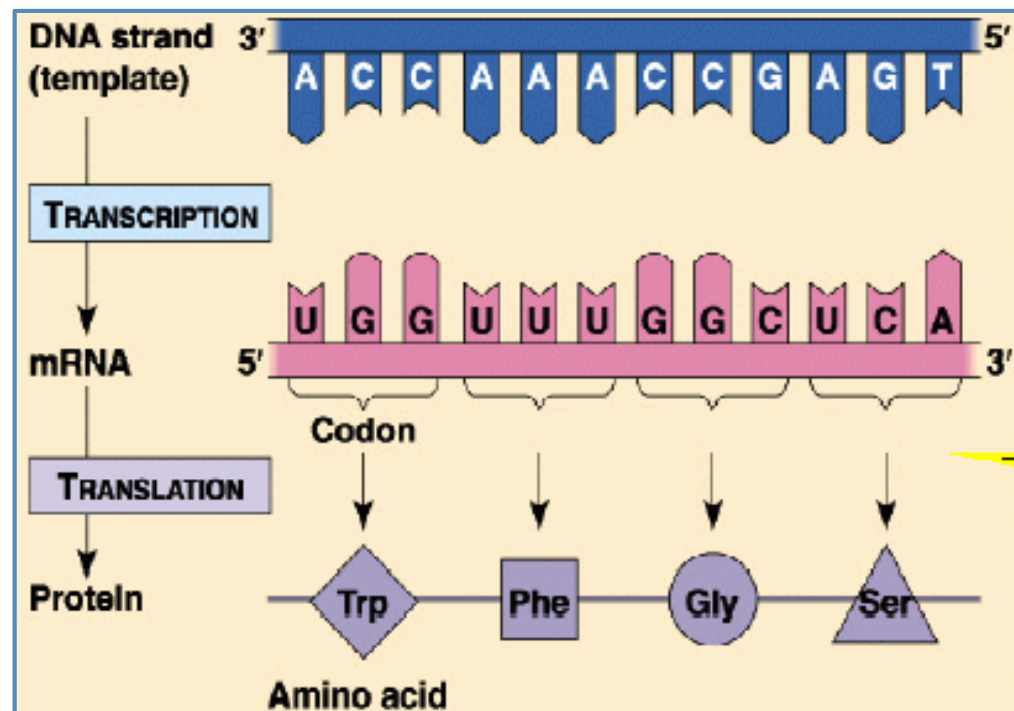
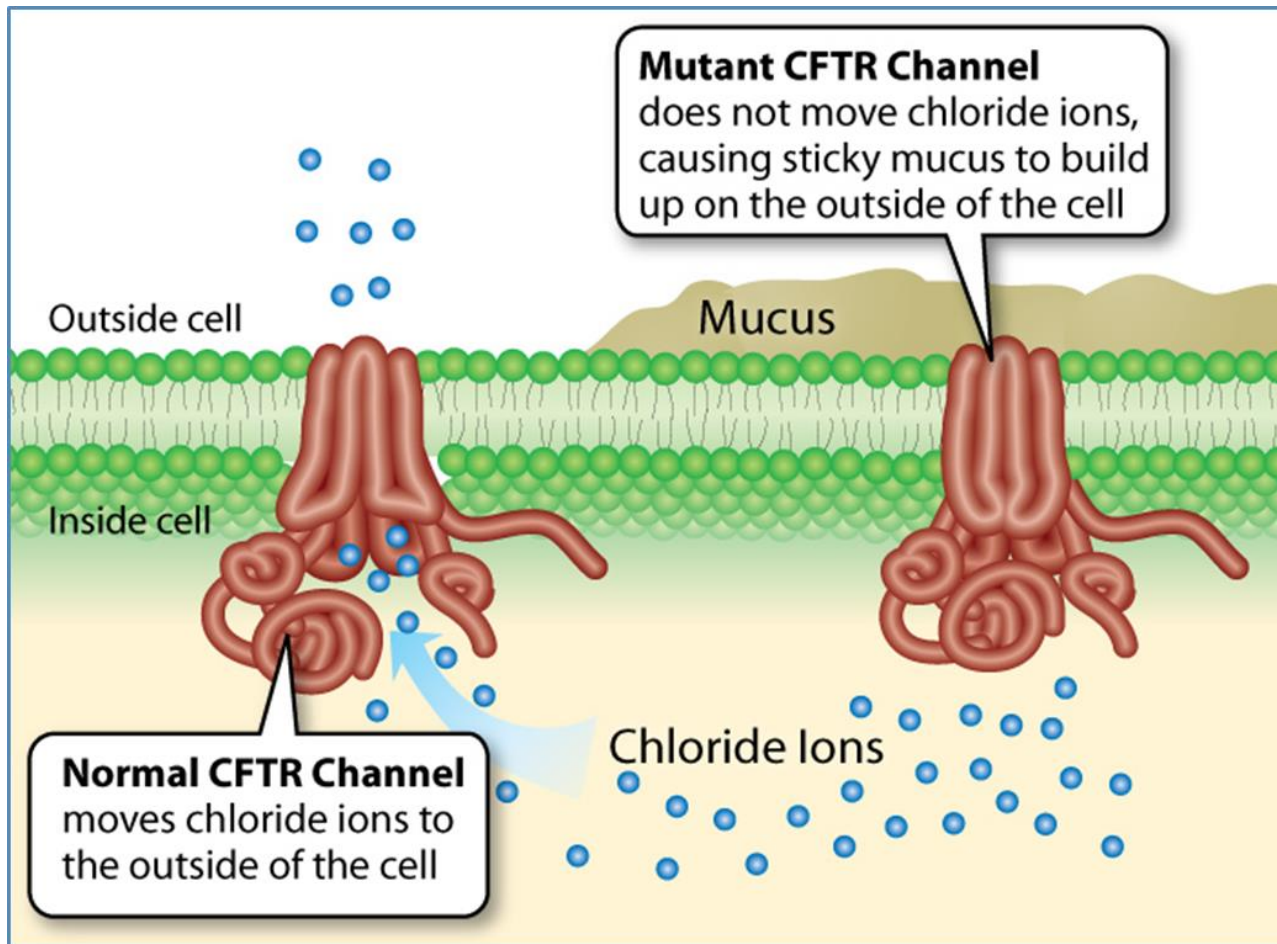


Image credit from Harvey Mudd College
web page:
<http://fourier.eng.hmc.edu/bioinformatics/intro/node8.html>

NOT ALWAYS!

Altered genes can lead to altered proteins which can lead to disruptions in normal processes

NOT ALWAYS!





CATEGORIES OF DISEASES ATTRIBUTED TO GENES

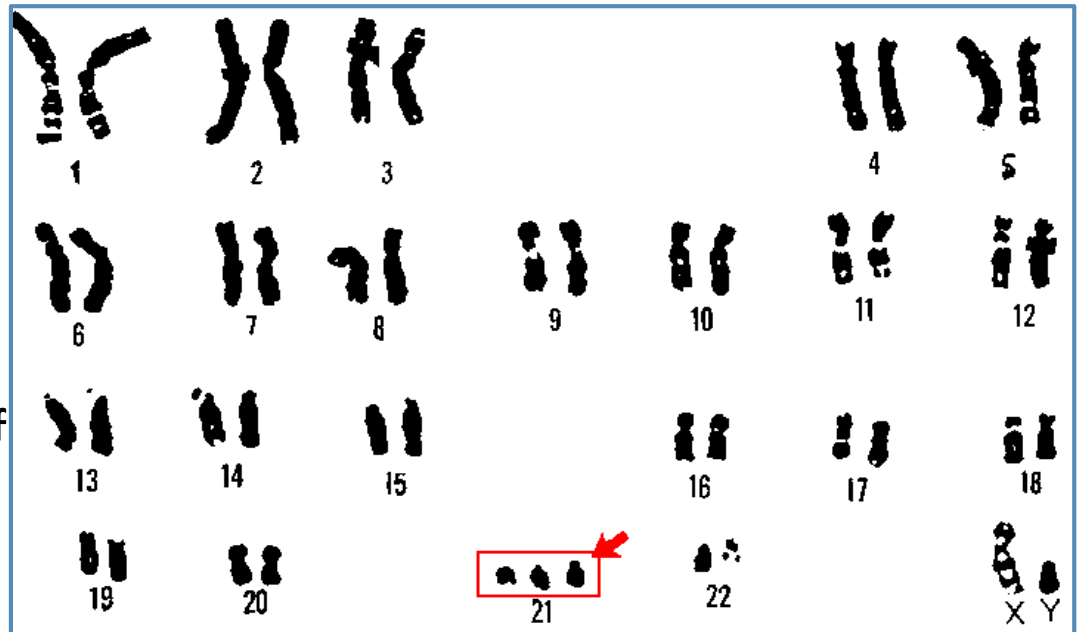
- Chromosomal Diseases
- Monogenic Diseases
- Multifactorial Diseases

Chromosomal Diseases

(Chromosomal Alterations)

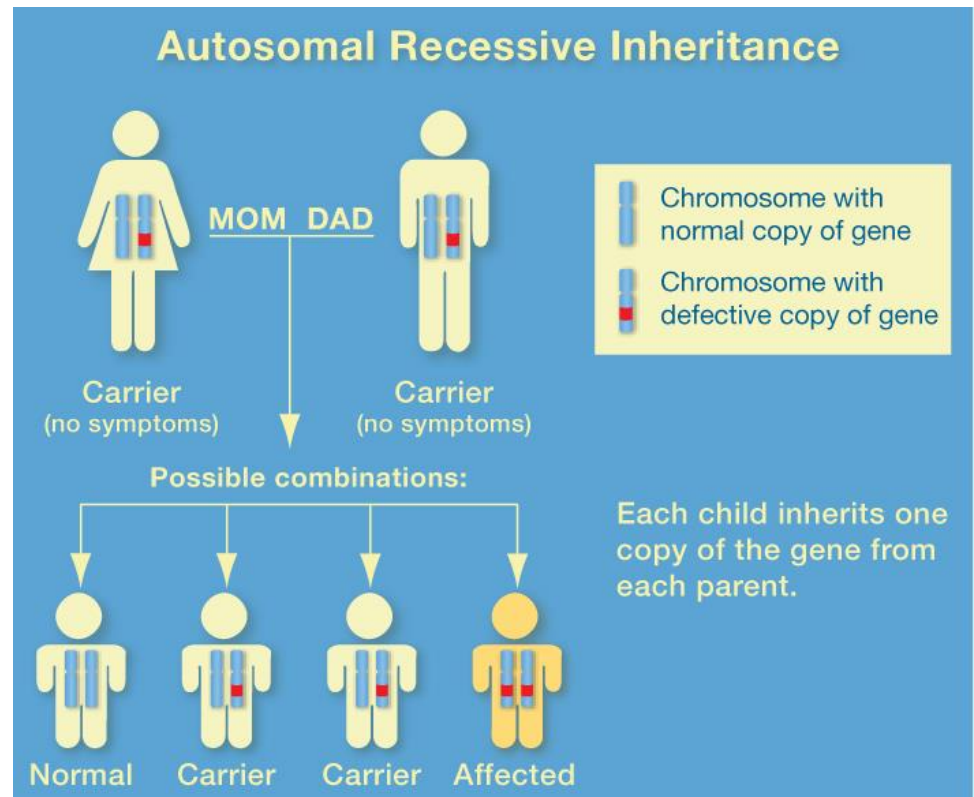
- An individual may have a missing chromosome, extra copies of a chromosome, or a portion of a chromosome may be deleted, duplicated, or translocated.
- Alteration may be inherited or *de novo*. Most originate in the egg or sperm.

- Examples: **Down's syndrome** (extra copy of chromosome 21) or **Prader-Willi syndrome** (microdeletion from short arm of chromosome 15)



Monogenic Diseases/ Mendelian Diseases

- Single-gene diseases follow the patterns of inheritance that Mendel discovered in his studies of pea plants.
- These rare inherited diseases tend to be caused by mutations in a single gene.
- Examples: cystic fibrosis, sickle-cell anemia, muscular dystrophy, and Huntington's disease.



Multifactorial Diseases

- Complex diseases are caused by variation in many genes. They may also be influenced by environmental factors.
- The vast majority of human diseases fall into this category.
- Identifying the genes that contribute to these diseases has been difficult.
- Examples: cardiovascular disease, cancer, diabetes, and a number of birth defects and psychiatric disorders.

Multifactorial Disease!



**"Your weight problem is partly genetic
and partly Boston Cream pie."**

Type 2 Diabetes: A Multifactorial Disease

According to a 2016 review article by Kaul and Ali

- “Type 2 diabetes (T2D) is a multifactorial anomaly involving **57 genes** located on 16 different chromosomes and **136 single nucleotide polymorphisms (SNPs)**.”
- “Genetic components have their own **pathways** encompassing insulin secretion, resistance, signaling, and β -cell dysfunction.”
- “**Environmental factors** include epigenetic changes, nutrition, intrauterine surroundings, and obesity.”
- “In addition, **ethnicity** plays a role in conferring susceptibility to T2D.”

What Can I Blame My Parents For?

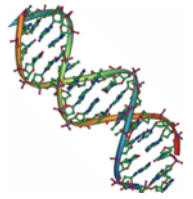
Heritability Estimates for Complex Traits

Bone Mineral Density	50-85%
Osteoarthritis	50%
Coronary artery disease	40-60%
Breast Cancer	25-45%
Neuroticism	6-15%
Ulcerative colitis	4-15%

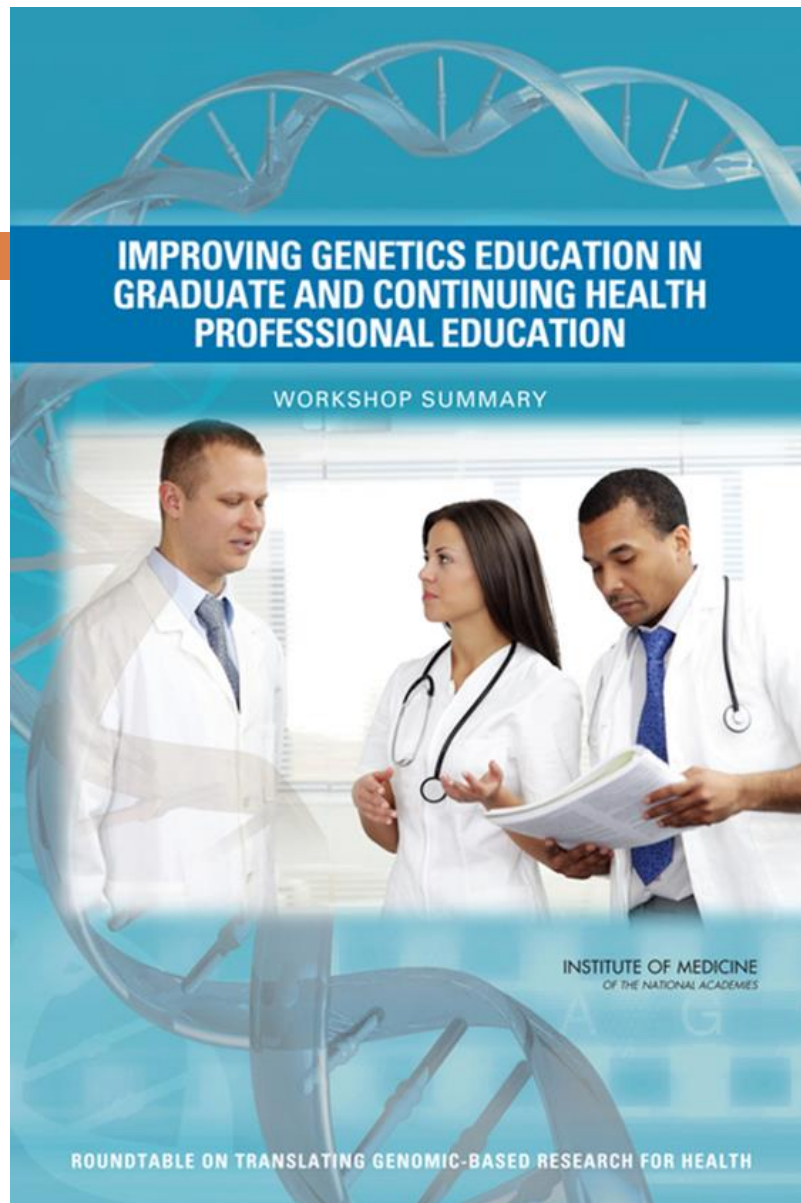
Heritability estimate – genetics accounts for what % of a person's susceptibility to a condition. Complex traits also due to other biological and environmental factors.

Numbers gathered from various recent articles.

How Are Changes in Genetics Affecting Health Care?



- Researchers learn more about genes and variants and disease risk every day.
- Capabilities for precision medicine are increasing.
- Health care providers **other** than medical geneticists and genetic counselors are dealing with genetic information.
- Clinicians may not have had much (recent) training in genetics.
- Genetic testing is a subject that patients may raise.
- Translating research findings to the clinic – do any of them apply to my patients?



“Despite the growing use of genomic applications in clinical practice, health professional knowledge about genomic information and confidence in using it have not kept pace....

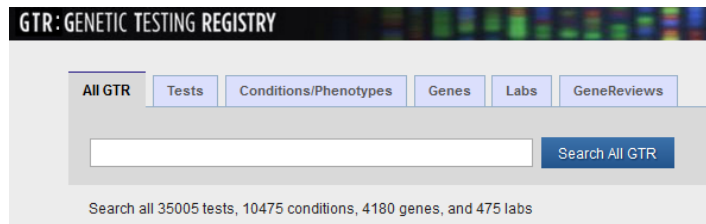
Many health care providers do not have either the knowledge or the tools they need in order to apply genetic information in their day-to-day practices.

This lack of support is contributing to a substantial delay in the translation of genetic research findings, when appropriate, into improvement in patient outcomes within the health care system.”

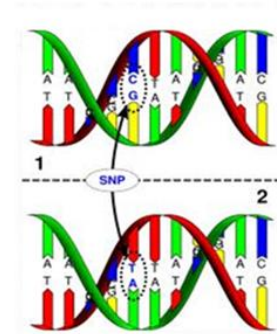
— Institute of Medicine 2015 report

Four Areas Where Genetics Is Intersecting Health Care

Diagnostic Testing

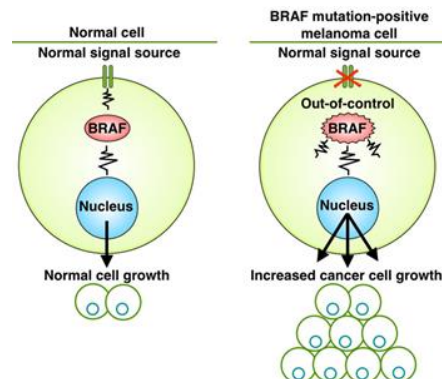


Single Nucleotide Polymorphisms



Graphic by Diane Rein – modified from Science Magazine, December 21, 2007

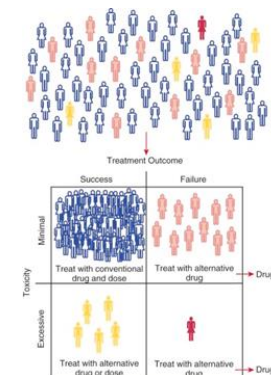
Tumor Genomic Testing



[Image credit Incyte Pathology blog:](http://incytepathology.blogspot.com)

<https://incytepathology.wordpress.com/2012/04/10/braf/>

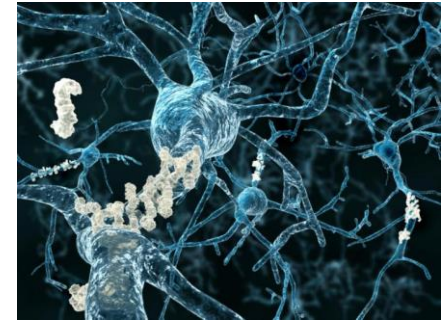
Pharmacogenomics



(Adapted from Yaffe SJ, Aranda JV: *Neonatal and pediatric pharmacology*, ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)

1. Diagnostic Testing – Does He Have Alzheimer's Disease?

Clinicians Don't Test Everyone.



Practice guidelines recommend testing for 3 genes associated with early onset AD in these 3 populations:

- 1) symptomatic patients with early onset AD;
- 2) individuals with a family history of dementia with one or more cases of early onset AD;
- 3) individuals with a relative affected by a known mutation of *APP*, *PSEN1*, or *PSEN2*.

Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. 2011. PMID:21577118

Beta-amyloid plaques picture: <https://www.flickr.com/photos/35049835@N00/16867428955>

The Answer to a Genetic Test Is Often Something Other Than Yes or No.

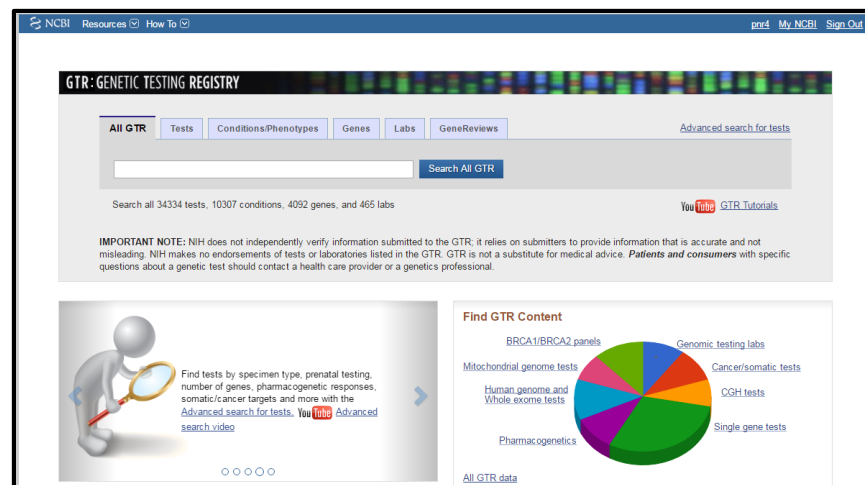
Labs Typically Report an Individual's Genetic Test Results Using Five Categories

1. Disease-causing mutation found.
2. Mutation found is **likely** disease-causing.
3. Mutation found is **probably** benign and not disease causing.
4. Mutation is known to be benign and does not cause disease.
5. Mutation is a “Variant of **Unknown Significance**” (VUS).

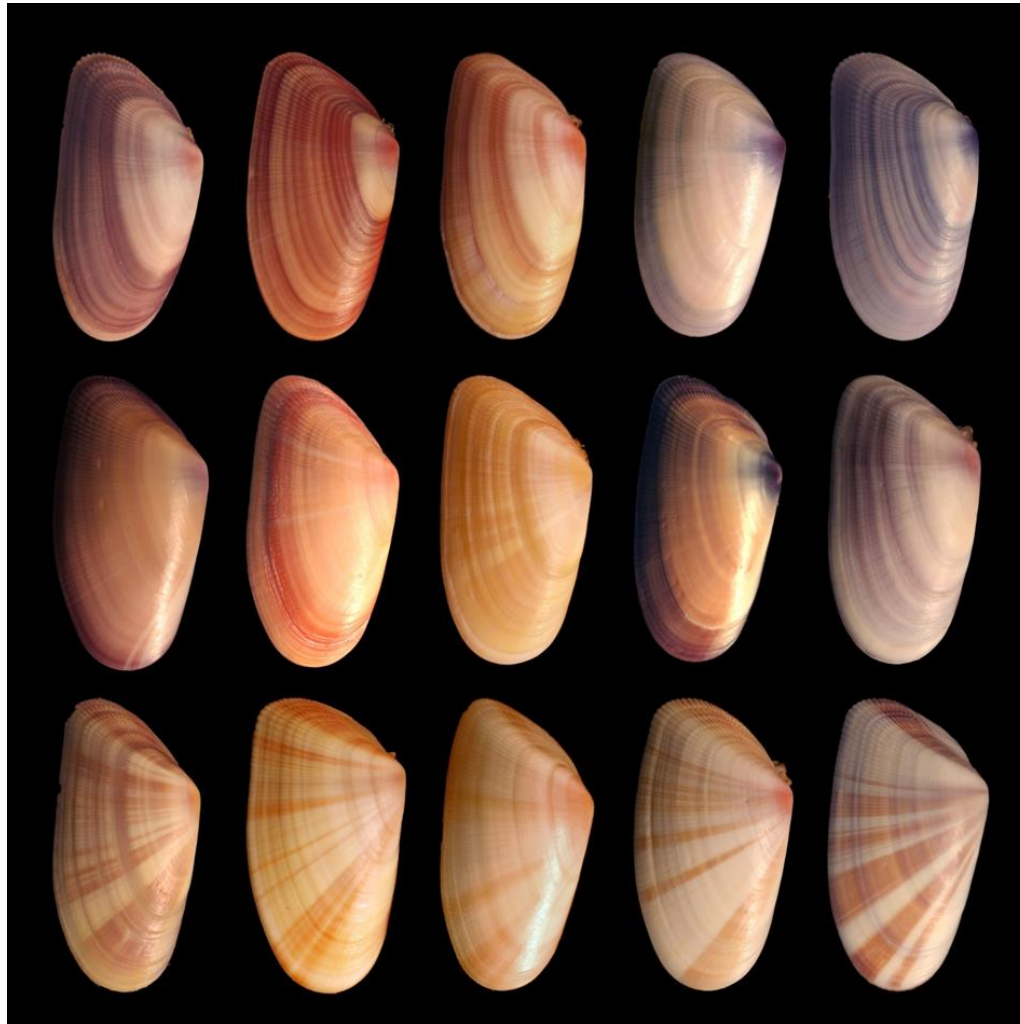


Genetic Test Results Require Interpretation

- ❑ Clinicians don't order genetic tests unless the results are likely to improve patient management.
- ❑ Typically Medical Geneticists and Genetic Counselors are the clinicians who are most qualified to order and interpret genetic tests.

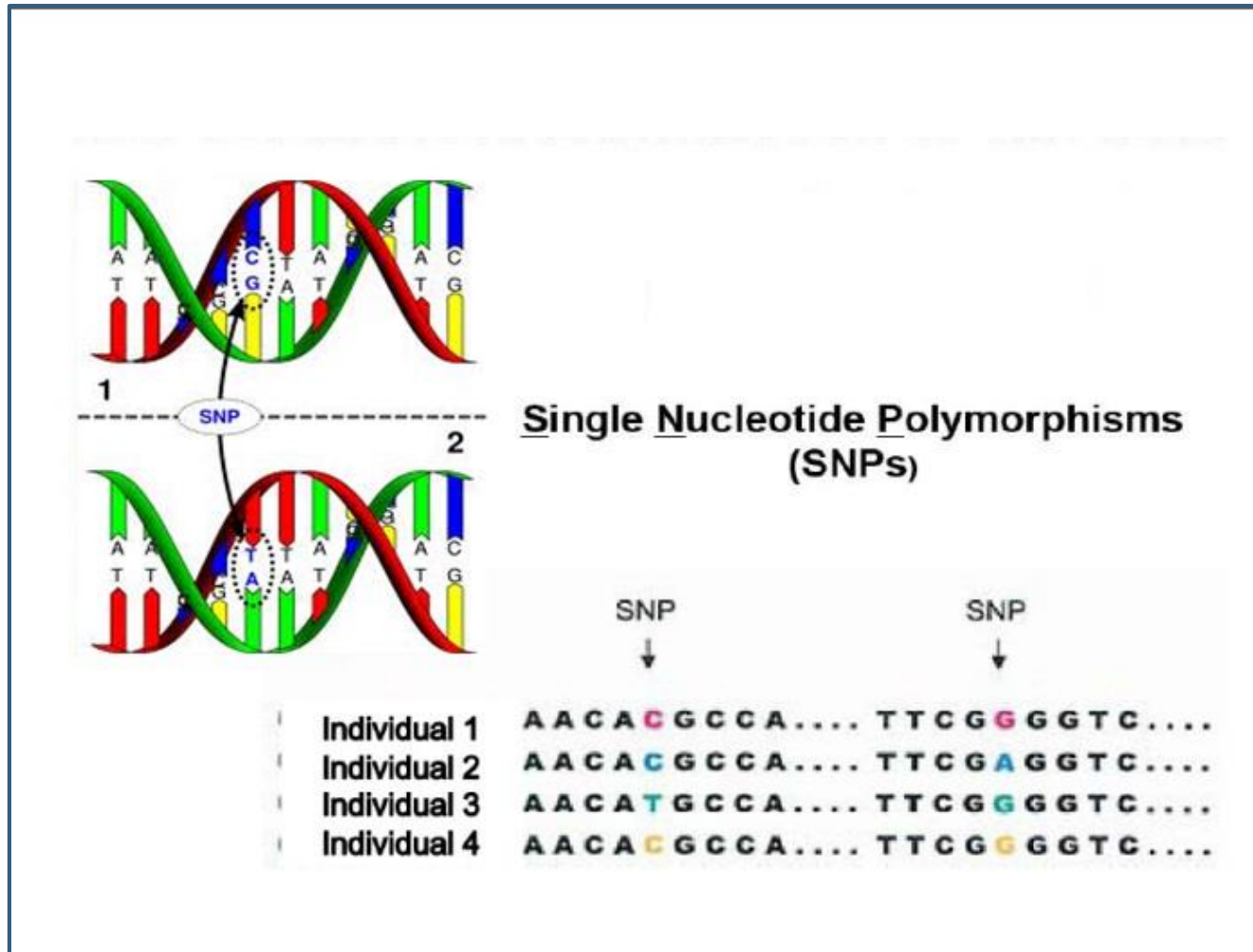


Polymorphism in Nature



By Debivort - Own work by Author, CC BY-SA 3.0, <https://commons.wikimedia.org/w/index.php?curid=1626674>

2. Genetic Variants – Single Nucleotide Polymorphisms



Over 1,600 SNPs Have Been Identified in the BRCA1 Gene.

Here is one of those SNPs.

Rs55770810

rs55770810, also known as R1699W, is a SNP in the **BRCA1** gene. The more common (C) allele encodes the amino acid arginine (R), while the rare (T) allele encodes a tryptophan (W).

An analysis of sequence variants of unknown clinical significance in the **BRCA1** and **BRCA2** genes concluded that this SNP was among the top 10 (over both genes) likely to lead to **breast cancer**, with a calculated odds of over 1,000:1 against this just being a spurious association. Although the clinical importance has not been proven, this may still be of use for genetic counseling.[PMID 17924331]

This SNP is also represented on some 23andMe microarrays as **i5010082**.

<https://www.snpedia.com/index.php/Rs55770810>

Categories: [Is a snp](#) | [In dbSNP](#) | [SNPs on chromosome 17](#) | [Has genotype](#) | [On chip 23andMe v3](#) | [On chip 23andMe v4](#) | [On chip Ancestry v2](#)

Orientation	minus	
Stabilized	minus	
Geno	Maq	Summary
(C;C)	0	normal
(C;T)	5	carrier of BRCA1 variant likely to be pathogenic
(T;T)	5	carrier of two copies of BRCA1 variant; likely to be at higher risk for breast/ovarian cancer
Reference	GRCh38 38.1/141	
Chromosome	17	
Position	43063931	
Gene	BRCA1	
is a	snp	

In the **BRCA1** gene – which is **193,689** nucleotides long – if this **1 particular nucleotide** is a T instead of a C, a person is more likely to get breast cancer.

BRCA1 SNPs –

“You have the breast cancer gene.”

- Approximately 500 of the 1,600+ known BRCA1 variants have been classified as **causal**.
- What should a person with a **BRCA1 variant that is causal** expect?
 - ▣ Increased risk of developing breast and/or ovarian cancer at an earlier age
 - ▣ Lifetime risk of breast cancer is 80 to 90%
 - ▣ Lifetime risk of ovarian cancer is 40 to 50%
 - ▣ Increased risk of bilateral breast cancer

Variants of Unknown Significance (VUSs)

Yes! A variant (SNP) is present in a gene. (We don't typically see that nucleotide in that location.)

No! We don't know what the clinical significance is. It could be benign, or it could be pathogenic.

A VUS in a lab report really is UNKNOWN.



After more evidence is collected, VUSs can often be categorized as benign or pathogenic.

Clinicians Are Concerned with Clinically Actionable Variants

- If you have a BRCA1 pathogenic variant, clinician may be able to provide:
 - ▣ Closer surveillance (MRI in addition to mammogram)
 - ▣ Surgery (if warranted)
 - ▣ Chemoprevention
 - ▣ Genetic Counseling
- Often the significance of a gene variant isn't known, or there isn't a helpful clinical way to address a gene variant.

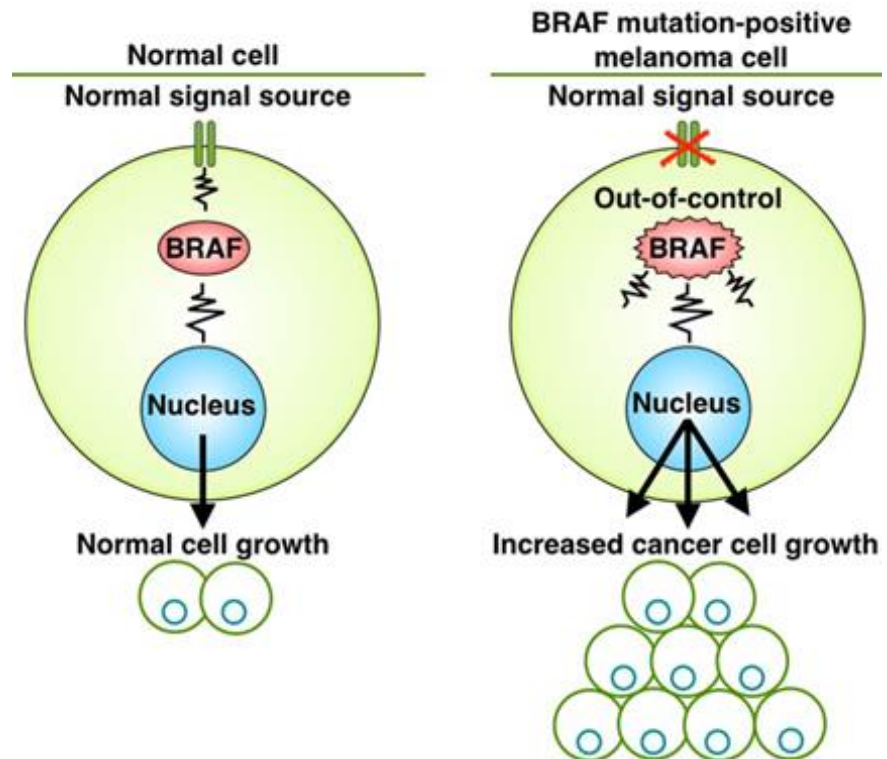


CLINICALLY
ACTIONABLE

3. Tumor Genomic Testing For Targeted Therapy

1. Researchers study genetic differences between tumor cells and normal cells.
2. Some tumor cells divide rapidly because their BRAF gene is not functioning properly.
3. Drugs are developed to target cells with this particular BRAF mutation.

Melanoma Cell With a BRAF V600 Mutation



NATIONAL CANCER INSTITUTE PRECISION MEDICINE IN CANCER TREATMENT

Discovering unique therapies that treat an individual's cancer based on the specific genetic abnormalities of that person's tumor.



www.cancer.gov

PRECISION MEDICINE

Image credit [Cancer.gov](http://www.cancer.gov/research/key-initiatives/precision-medicine): <http://www.cancer.gov/research/key-initiatives/precision-medicine>

If Your Tumor Cells Have This Mutation, Then We'll Prescribe This Drug

Some Drugs Are
Approved Along
With “Companion
Diagnostic Tests”

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TAFINLAR safely and effectively. See full prescribing information for TAFINLAR.

TAFINLAR[®] (dabrafenib) capsules, for oral use
Initial U.S. Approval: 2013

-----RECENT MAJOR CHANGES-----

Indications and Usage (1.2)	11/2015
Dosage and Administration (2)	11/2015
Warnings and Precautions (5)	11/2015

-----INDICATIONS AND USAGE-----

- TAFINLAR is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. (1.1, 2.1, 14.1)
- TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1.2, 2.1, 14.2)

Limitation of Use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma. (1.3, 5.2)

-----DOSAGE AND ADMINISTRATION-----

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent. (2.1)
- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with trametinib. (2.1)

Precision Medicine in Oncology

Table 1. Drug Targets and Their FDA-Approved Companion Diagnostic Tests

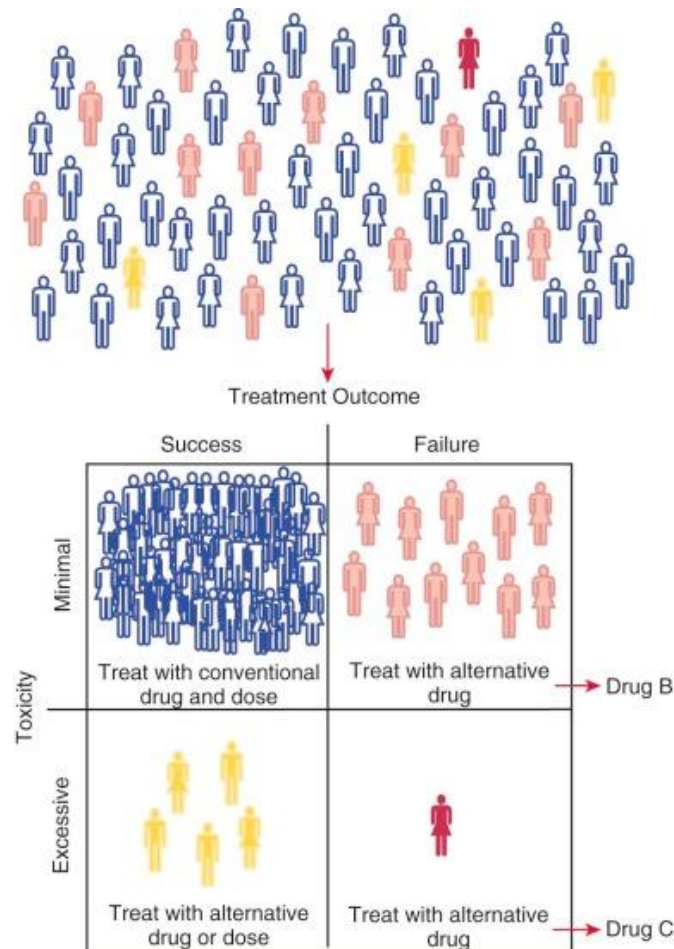
Drug	Target ^a	Indication ^a	Diagnostic Tests ^a
Trastuzumab	HER2/Neu Amplification ^b	Breast Cancer	Bond Oracle Her2 IHC System INFORM HER2 DUAL ISH DNA Probe Cocktail INSITE HER-2/NEU KIT SPOT-LIGHT HER2 CISH Kit PATHWAY ANTI-HER-2/NEU (4B5) Rabbit Monoclonal Primary Antibody INFORM HER-2/NEU
		Localized, lymph node-negative breast cancer	
		Stage II, lymph node-positive breast cancer	HER2 CISH PharmDx Kit PATHVYSION HER-2 DNA Probe Kit
Trastuzumab/Pertuzumab/ Ado-Trastuzumab Emtansine		Breast cancer & gastric cancer	HER2 FISH PharmDx Kit HERCEPT
Crizotinib	ALK rearrangement	NSCLC	VENTANA ALK (D5F3) CDx Assay VYSIS ALK Break Apart FISH Probe Kit
Afatinib	EGFR Exon 19 deletion or L858R	NSCLC	<i>therascreen</i> EGFR RGQ PCR Kit cobas EGFR Mutation Test
Erlotinib			<i>therascreen</i> EGFR RGQ PCR Kit
Gefitinib			cobas EGFR Mutation Test v2 ^c
Osimertinib	EGFR T790M	NSCLC	DAKO EGFR PharmDx Kit
Cetuximab/Panitumumab	EGFR Expression KRAS Codon 12/13	CRC	cobas KRAS Mutation Test <i>therascreen</i> KRAS RGQ PCR Kit THxID BRAF Kit ^d cobas 4800 BRAF V600 Mutation Test
Dabrafenib/Trametinib	BRAF V600E	Melanoma	PD-L1 IHC 22C3 PharmDx
Vemurafenib			DAKO C-kit PharmDx
Pembrolizumab	PD-L1 Expression	NSCLC	KIT D816V Mutation Detection by PCR
Imatinib Mesylate	c-Kit	GIST	PDGFRB FISH
	KIT D816V	ASM	BRACAnalysis CDx
	PDGFRB	MDS/MPD	VYSIS CLL FISH Probe Kit
Olaparib	Germline BRCA1/BRCA2	Ovarian cancer	
Venetoclax	17p deletion	CLL	

4. Pharmacogenomics: Should We Prescribe You a Little, a Lot, or None At All?

Pharmacogenomics

Purpose: Study how genes affect an individual's responses to drugs.

Goal: Predict who will benefit from a medication, who will not respond at all, and who will experience adverse drug reactions.



Plavix (Clopidogrel)

- Anti-platelet drug – inhibits blood clots which can lead to heart attack and stroke.
- Some people have CYP2C19 variants that cause them to metabolize Plavix slowly.
- Slow metabolism of Plavix = increased risk of clotting/adverse events.
- Physicians will prescribe different antiplatelet drugs for these people.



BOXED WARNING [\(WHAT IS THIS?\)](#)

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1)] ...

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)]. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see [CLINICAL PHARMACOLOGY \(12.5\)](#)]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see [DOSAGE AND ADMINISTRATION \(2.3\)](#)].



FDA-Approved Drugs with Pharmacogenomic Information in Their Labels

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

165 drugs on this FDA list as of October 2016.

Sometimes genetic testing is mandatory for prescribing a drug.

The table below lists FDA-approved drugs with pharmacogenomic information in their labeling. The labeling for some, but not all, of the products includes specific actions to be taken based on the biomarker information. Pharmacogenomic information can appear in different sections of the labeling depending on the actions. For more information, please refer to the appropriate labeling guidance.

Therapeutic areas include anesthesiology, cardiology, dermatology, endocrinology, gastroenterology, hematology, infectious diseases, and psychiatry. The largest number are oncology drugs.

Barriers to Use of Pharmacogenomic Testing in Clinical Practice

Table 2: Practical issues involved in clinical implementation of pharmacogenomic testing in healthcare system.

Issue	Challenge
Test performance	Reasonable turnaround time for delivery of test result
Interpretation of result	Not a straightforward normal versus abnormal interpretation Education of clinicians is crucial to proper use
Education of health professionals	Variable time and content devoted to educating future clinicians within health professional schools Overwhelming information for most current practicing clinicians
Cost reimbursement by payers	Almost exclusively based on proof of cost-effectiveness
Acceptance by clinicians	Potential additional workload Potential legal liability Health disparity concern for patient
Acceptance by patients	Privacy and discrimination concern Health disparity concern Ownership of genetic information

Y. W. Francis Lam, "Scientific Challenges and Implementation Barriers to Translation of Pharmacogenomics in Clinical Practice," *ISRN Pharmacology*, vol. 2013, Article ID 641089, 2013.

Survey of >10,000 US physicians: "Although 98% of all respondents agreed that the genetic profile of a patient could influence drug therapy decision, only 29% had received some pharmacogenomics education during their medical training, and **only 10% felt they were adequately trained to apply the knowledge in clinical practice.**"

E. J. Stanek, C. L. Sanders, K. A. Taber et al., "Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey," *Clinical Pharmacology and Therapeutics*, vol. 91, pp. 450–458, 2012.

1000 Genomes Project



[Credit Flickr - https://www.flickr.com/photos/trevor-dennis/](https://www.flickr.com/photos/trevor-dennis/)

- ❑ Conducted to permit the study of genetic variation in the human population. (Completed 2015.)
- ❑ Analyzed 2,504 genomes from 26 populations across 5 continental regions.
- ❑ Increased diversity in genetic databases still needed!

Clinical Uses of Genetic Tests

GENETIC TESTING
NHGRI FACT SHEETS
genome.gov

Genetic Tests Can Help to:

- Diagnose Your Disease**
- Pinpoint Genetic Factors That Caused Your Disease**
- Predict How Severe Your Disease Might Be**
- Choose the Best Medicine and Correct Dose**
- Discover Genetic Factors That Increase Your Disease Risk**
- Find Genetic Factors That Could Be Passed to Your Children**
- Screen Newborns for Certain Treatable Conditions**

National Human Genome Research Institute

Jean's Genetic Testing Timeline

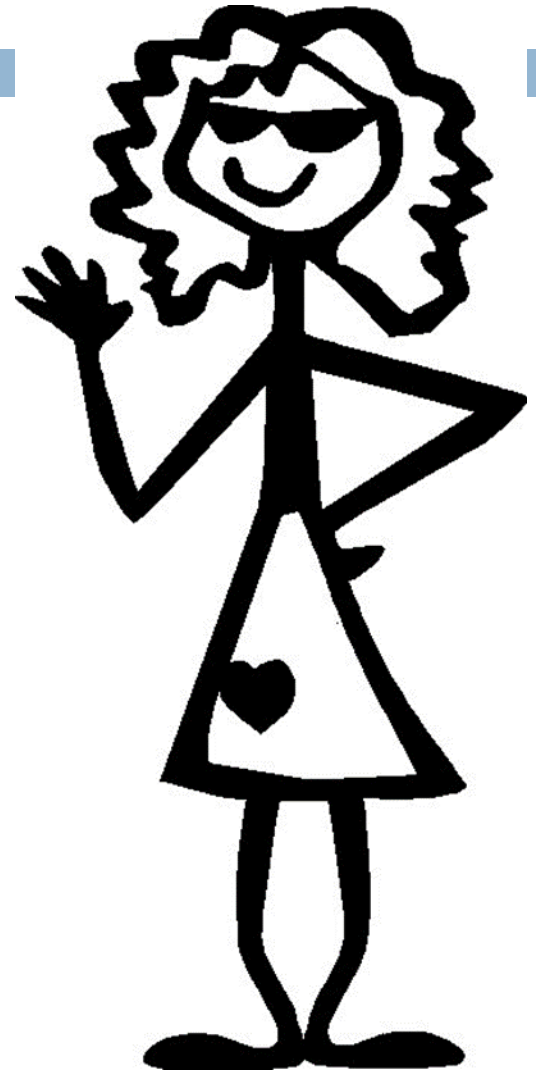
Age 1 Day: newborn testing for a few serious childhood diseases

Age 30: carrier testing (with her partner) before getting pregnant

Age 35: predictive testing when sister develops breast cancer at a young age

Age 45: direct-to-consumer testing to investigate ancestry

Age 65: pharmacogenomics testing when Plavix (anti-platelet drug) was not effective



Repeat Testing May Yield Different Results!

What genes and what variants did you test for?

- Different tests offered for the same conditions.
- Knowledge always changing.

Might not have enough examples in the database to determine associations between specific variants and specific conditions.

Might not have enough examples of people like you in the database.

Possibility of false positive and false negative results.





TAKE A BREAK!

Selected Genetic Medicine Databases for Clinicians

MedGen portal	Medical genetics information compiled from GeneReviews, OMIM, ClinVar, Genetic Testing Registry, practice guidelines, and PubMed. Links to consumer information.
Gene Reviews	Point-of-care information for inherited conditions - diagnosis, management, and genetic counseling information. Peer-reviewed chapters. Search by gene or disorder.
OMIM	Overviews of Mendelian disorders and genes associated with disease. Can search by symptom.
GTR: Genetic Testing Registry	Tests for clinical use and genetic research. Individual genes and gene panels. Information submitted by test providers.
ClinVar	Variants found in patient samples along with assertions regarding the variants' clinical significance. Includes level of evidence available.
PharmGKB	Information on the impact of human genetic variations on drug response. Includes drug dosing guidelines.

UW Genetic Medicine Guide

University of Washington Libraries / Library Guides / HSL / Genetic Medicine

Genetic Medicine: Genetic Medicine

Genetic information resources for clinicians

Genetic Medicine Resources: Starting Points for Clinicians

MedGen



GeneReviews



Genetic Testing Registry



PharmGKB



OMIM



PubMed - Medical Genetics



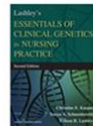
Clinical Genetics E-Books



**Thompson and Thompson
Genetics in Medicine, 8th ed.
(2016)** by Robert Nussbaum;
Roderick R. McInnes;
Huntington F. Willard [W](#)



**Clinical Genomics: Practical
Applications in Adult Patient
Care** by Michael Murray; Mark
W. Babyatski; Monica A.
Giovanni [W](#)



**Lashley's Essentials of Clinical
Genetics in Nursing Practice
(2015)** [W](#)



**Genomic and Personalized
Medicine (2013)** by Huntington
Willard [W](#)



**Emery and Rimoin's Principles
and Practice of Medical
Genetics, 6th ed (2013)** by
David L. Rimoin [W](#)

Genetic Competencies & Educational Resources for Clinicians

• Genetic Competency Guidelines & Educational

Key Genetic Medicine Resources

- **MedGen**
 - o Medical genetics information compiled from GeneReviews, OMIM, ClinVar, Genetic Testing Registry, and PubMed.
 - o Search for a gene, genetic disorder, or clinical feature to find summaries of clinical conditions.
 - o Links to practice guidelines.
- **Gene Reviews**
 - o Point-of-care information for inherited conditions - diagnosis, management, and genetic counseling information.
 - o Peer-reviewed chapters typically focus on a single gene or phenotype/disorder.
- **OMIM (Online Mendelian Inheritance in Man)**
 - o Overviews of Mendelian disorders and genes associated with disease.
 - o Search for symptoms/physical features to find clinical synopses of conditions.
- **ClinVar**
 - o Variants found in patient samples
 - o Assertions regarding variants' clinical significance.

Pharmacogenomics Resources

- **PharmGKB: Pharmacogenomics Knowledge Base**
 - o Curated information on the impact of human genetic variations on drug responses.
 - o Drug dosing guidelines.
- **PharmGKB's Level 1A & 1B Clinical Annotations**
 - o Clinical variant-drug annotations with the highest level of evidence.

• FDA Table of Pharmacogenomic Biomarkers in

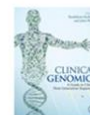
Medical Genetics Literature in PubMed

Two ways to efficiently identify PubMed references relating to medical genetics:

1. Use the **Medical Genetics clinical filter** which can be found under "Clinical Queries"
2. Locate a **MeSH term** that describes the topic you're interested in, and then add the "genetics" subheading. For example:
"Cardiomyopathy, Hypertrophic/genetics"
[\[Mesh\]](#)

Genetic Tests

- **NIH Genetic Testing Registry (GTR)**
 - o Tests for clinical use and genetic research.
 - o Information submitted by test providers.
 - o Use Advanced Search to specify multiple criteria.
- **GeneTests**
 - o Search by disorder or gene to find available clinical genetic tests.
- **NextGxDx**
 - o Commercial database of genetic tests.
- **Tier Table Database (CDC Office of Public Health Genomics)**
 - o Ranking of genomic tests, and family health history applications, by levels of evidence.



Clinical Genomics (2015) by
Shashikant Kulkarni (Editor);
John Pfeifer (Editor) [W](#)
Provides an overview of the
next-generation sequencing
(NGS) technologies that are
used in clinical diagnostic laboratories. Also
focuses on the challenges of diagnostic

Genetic Medicine Guide —

<http://guides.lib.uw.edu/hsl/geneticmedicine>

PubMed Medical Genetics Query

PubMed Clinical Queries

Results of searches on this page are limited to specific clinical research areas. For comprehensive searches, use [PubMed](#) directly.

ventricular hypertrophy

Search

Clinical Study Categories

Category: Therapy
Scope: Broad

Systematic Reviews

Results: 5 of 277

Heart failure-potential new targets for therapy.

Wang JJ, Rau C, Avetisyan R, Ren S, Romay MC, Stolin G, Gong KW, Wang Y, Lusis AJ.
PLoS Genet. 2016 Jul; 12(7):e1006038. Epub 2016 Jul 6.

A Long Term Follow-up Study of Carriers of Hypertrophic Cardiomyopathy Mutations.

McTaggart DR, Ogden KJ, Marathe JA.
Heart Lung Circ. 2016 May 20; . Epub 2016 May 20.

See all (9457)

Medical Genetics

Topic: All

Results: 5 of 5221

Genetic Dissection of Cardiac Remodeling in an Isoproterenol-Induced Heart Failure Mouse Model.

Wang JJ, Rau C, Avetisyan R, Ren S, Romay MC, Stolin G, Gong KW, Wang Y, Lusis AJ.
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Multicenter Female Fabry Study (MFFS) - clinical survey on current treatment of females with Fabry disease.

Lenders M, Hennermann JB, Kurschat C, Rolfs A, Canaan-Kühl S, Sommer C, Üçeyler N, Kampmann C, Karabul N, Giese AK, et al.
Orphanet J Rare Dis. 2016 Jun 29; 11(1):88. Epub 2016 Jun 29.

Long-term enzyme replacement therapy for Fabry disease: efficacy and unmet needs in cardiac and renal outcomes.

Kim JH, Lee BH, Hyang Cho J, Kang E, Choi JH, Kim GH, Yoo HW.
J Hum Genet. 2016 Jun 23; . Epub 2016 Jun 23.

The CYBA Gene (+)49A>G Polymorphism (rs7195830) Is Associated with Hypertension in Patients with Coronary Artery Disease.

Nowak T, Niemiec P, Górczyńska-Kosiorz S, Balcerek A, Iwanicki T, Krauze J, Grzeszczak W, Ochalska-Tyka A, Iwanicka J, Zak I.
Biomed Res Int. 2016; 2016:1539871. Epub 2016 May 24.

See all (5221)

Medical Genetics

Topic: All

Results: 5 of 5221

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Biomed Res Int. 2016; 2016:1539871. Epub 2016 May 24.

See all (5221)

Genetics Subheading

NCBI Resources How To

MeSH MeSH Limits Advanced

Full Send to:

Hypertrophy, Left Ventricular

Enlargement of the LEFT VENTRICLE of the heart. This increase in ventricular mass is attributed to sustained abnormal pressure or volume loads and is a contributor to cardiovascular morbidity and mortality.

Year introduced: 1993

PubMed search builder options

[Subheadings:](#)

<input type="checkbox"/> analysis	<input type="checkbox"/> epidemiology	<input type="checkbox"/> physiopathology
<input type="checkbox"/> anatomy and histology	<input type="checkbox"/> ethnology	<input type="checkbox"/> prevention and control
<input type="checkbox"/> blood	<input type="checkbox"/> etiology	<input type="checkbox"/> psychology
<input type="checkbox"/> chemically induced	<input checked="" type="checkbox"/> genetics	<input type="checkbox"/> radiography
<input type="checkbox"/> classification	<input type="checkbox"/> history	<input type="checkbox"/> radionuclide imaging
<input type="checkbox"/> complications	<input type="checkbox"/> immunology	<input type="checkbox"/> radiotherapy
<input type="checkbox"/> congenital	<input type="checkbox"/> metabolism	<input type="checkbox"/> rehabilitation
<input type="checkbox"/> cytology	<input type="checkbox"/> microbiology	<input type="checkbox"/> statistics and numerical data
<input type="checkbox"/> diagnosis	<input type="checkbox"/> mortality	<input type="checkbox"/> surgery
<input type="checkbox"/> diet therapy	<input type="checkbox"/> nursing	<input type="checkbox"/> therapy
<input type="checkbox"/> drug therapy	<input type="checkbox"/> organization and administration	<input type="checkbox"/> ultrasonography
<input type="checkbox"/> economics	<input type="checkbox"/> parasitology	<input type="checkbox"/> urine
<input type="checkbox"/> embryology	<input type="checkbox"/> pathology	<input type="checkbox"/> veterinary
<input type="checkbox"/> enzymology	<input type="checkbox"/> physiology	<input type="checkbox"/> virology

NCBI's MedGen Portal

<http://www.ncbi.nlm.nih.gov/medgen>



MedGen

Organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.

MedGen: NCBI Portal to Medical Genetics Content

- New and evolving NCBI resource. Development began in 2012.
- Information about human disorders and features or symptoms that have a genetic component.
- Designed for health care professionals and the medical genetics community.
- Compiles information from multiple sources: GeneReviews, OMIM, Genetic Testing Registry, ClinVar, Genetics Home Reference, practice guidelines, and PubMed.

Good Search Strategy Is Following a Link from a PubMed Reference to MedGen

Format: Abstract ▾

Send to ▾

PLoS One. 2016 Jan 11;11(1):e0145832. doi: 10.1371/journal.pone.0145832. eCollection 2016.

Role of Lung Function Genes in the Development of Asthma.

Yamada H¹, Masuko H¹, Yataqai Y¹, Sakamoto T¹, Kaneko Y¹, Iijima H², Naito T², Noguchi E³, Konno S⁴, Nishimura M⁴, Hirota T⁵, Tamari M⁵, Hizawa N¹.

Author information

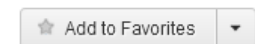
Abstract

Although our previous GWAS failed to identify SNPs associated with pulmonary function at the level of genomewide significance, it did show that the heritability for FEV1/FVC was 41.6% in a Japanese population, suggesting that the heritability of pulmonary function traits can be explained by the additive effects of multiple common SNPs. In addition, our previous study indicated that pulmonary function genes identified in previous GWASs in non-Japanese populations accounted for 4.3% to 12.0% of the entire estimated heritability of FEV1/FVC in a Japanese population. Therefore, given that many loci with individual weak effects may contribute to asthma risk, in this study, we created a quantitative score of genetic load based on 16 SNPs implicated in lower lung function in both Japanese and non-Japanese populations. This genetic risk score (GRS) for lower FEV1/FVC was consistently associated with the onset of asthma ($P = 9.6 \times 10^{-4}$) in 2 independent Japanese populations as well as with the onset of COPD ($P = 0.042$). Clustering of asthma patients based on GRS levels indicated that an increased GRS may be responsible for the development of a particular phenotype of asthma characterized by early onset, atopy, and severer airflow obstruction.

Full text links



Save items



Similar articles

- Heritability of pulmonary function estimated from genome-wide SNF [Respir Investig. 2015]
- Lower FEV1 in non-COPD, nonasthmatic subjects: as. [Int J Chron Obstruct Pulmon Di...
- Genome-wide association study of lung function phenoty [J Allergy Clin Immunol. 2014]
- Heritability of pulmonary function estimated from pedigree and whole-q [Front Genet. 2013]
- Review Lower limit of normal or FEV1/FVC < 0.70 in diagnosing COPD: ε [Respir Med. 2011]

See reviews...

See all...

Related information

Articles frequently viewed together

MedGen

References for this PMC Article

Free in PMC

MedGen

MedGen

Limits Advanced

Full Report ▾

Send to: ▾

Asthma, susceptibility to

MedGen UID: 358271 • Concept ID: C1869116 • Finding

Synonyms: ASTHMA, BRONCHIAL; ASTHMA-RELATED TRAITS, SUSCEPTIBILITY TO

Modes of inheritance: Autosomal recessive inheritance (HPO)

Genes (locations): ADRB2 (5q32); ALOX5 (10q11.21); CCL11 (17q12); HLA-G (6p22.1); HNMT (2q22.1); IL13 (5q31.1); MUC7 (4q13.3); PHE11 (13q14.2); PLA2G7 (6p12.3); SCGB3A2 (5q32); TNF (6p21.33)

OMIM®: 600807

Definition

Go to: ☺ ☹

Bronchial asthma is the most common chronic disease affecting children and young adults. It is a complex genetic disorder with a heterogeneous phenotype, largely attributed to the interactions among many genes and between these genes and the environment. Asthma-related traits include clinical symptoms of asthma, such as coughing, wheezing, and dyspnea; bronchial hyperresponsiveness (BHR) as assessed by methacholine challenge test; serum IgE levels; atopy; and atopic dermatitis (Laitinen et al., 2001; Illig and Wjst, 2002; Pillai et al., 2006). See 147050 for information on the asthma-associated phenotype atopy. [from OMIM]

Exploration of MedGen Together

MedGen


MedGen

Search

Limits

Advanced

Help



MedGen

Organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.

Using MedGen

- MedGen Quick Start
- List of Professional Guidelines
- Help
- MedGen Chapter in The NCBI Handbook
- Select condition and phenotype terms for ClinVar and GTR
- Frequently asked questions
- Downloads/FTP
- MedGen News

MedGen Tools

- 1000 Genomes Browser
- Variation

Other Resources

- ClinVar
- Gene
- Genetic Testing Registry (GTR®)
- GeneReviews®
- OMIM®
- RefSeqGene

Example searches

Name	achondroplasia[title]	As you type your query, names of genetic disorders used in the NIH Genetic Testing Registry (GTR) will be provided. If you do not make a selection from the menu that appears under the search box as you type, your query is processed by looking for a match on a word or phrase. * is used as the wild card, and that wild card can be used only at the end of a word.
Related gene	LMNB1[gene]	If you enter a gene symbol followed by [gene], the diseases caused by or with some association to that gene will be retrieved.
Clinical feature	short stature[clinical features]	If you enter the name of the feature followed by [clinical feature] the diseases with that feature will be retrieved.

MedGen Summary – Familial Cancer of Breast

MedGen

MedGen

Search

Limits Advanced

Help

Full Report ▾

Send to: ▾

Familial cancer of breast
MedGen UID: 87542 • Concept ID: C0346153 • Neoplastic Process

Synonyms: BARD1-Related Susceptibility to Breast Cancer; BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer; CHEK2-Related Breast Cancer; CHEK2-Related Susceptibility to Breast Cancer

Modes of inheritance: Heterogeneous (HPO)
Autosomal dominant inheritance (HPO)

SNOMED CT: Familial cancer of breast (254843006)

Genes (locations): AKT1 (14q32.33); ATM (11q22.3); BARD1 (2q35); BRCA1 (17q21.31); BRCA2 (13q13.1); BRIP1 (17q23.2); CASP8 (2q33.1); CDH1 (16q22.1); CHEK2 (22q12.1); ESR1 (6q25.1-25.2); HMMR (5q34); KRAS (12p12.1); NQO2 (6p25.2); PALB2 (16p12.2); PHB (17q21.33); PIK3CA (3q26.32); PPM1D (17q23.2); RAD51 (15q15.1); RAD54L (1p34.1); RB1CC1 (8q11.23); SLC22A18 (11p15.4); TP53 (17p13.1); TSG101 (11p15.1); XRCC3 (14q32.33)

OMIM®: 114480

⬆ Disease characteristics

Go to: ⌵ ⌶

Excerpted from the *GeneReview*: **BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer**
Hereditary breast and ovarian cancer syndrome (HBOC), caused by a germline pathogenic variant in BRCA1 or BRCA2, is characterized by an increased risk for breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer. The lifetime risk for these cancers in individuals with a pathogenic variant in BRCA1 or BRCA2: 40%-80% for breast cancer, 11%-40% for ovarian cancer, 1%-10% for male breast cancer. Up to 39% for prostate cancer, 1%-7% for pancreatic cancer. Individuals with BRCA2 pathogenic variants may also be at an increased risk for melanoma. Prognosis for BRCA1/2-related cancer depends on the stage at which the cancer is diagnosed; however, studies on survival have revealed conflicting results for individuals with germline BRCA1 or BRCA2 pathogenic variants when compared to controls. [from *GeneReviews*]

Full text of *GeneReview* (by section):
[Summary](#) | [Diagnosis](#) | [Clinical Characteristics](#) | [Genetically Related \(Allelic\) Disorders](#) | [Differential Diagnosis](#) | [Management](#) | [Genetic Counseling](#) | [Resources](#) | [Molecular Genetics](#) | [References](#) | [Chapter Notes](#)

Authors:
Nancie Petrucelli | Mary B Daly | Gerald L Feldman [view full author information](#)

⬆ Additional descriptions

Go to: ⌵ ⌶

From OMIM
Breast cancer (referring to mammary carcinoma, not mammary sarcoma) is histopathologically and almost certainly etiologically and genetically heterogeneous. Important genetic factors have been indicated by familial occurrence and bilateral involvement. <http://www.omim.org/entry/114480>

From GHR
Breast cancer is a disease in which certain cells in the breast become abnormal and multiply uncontrollably to form a tumor. Although breast

Table of contents

[Disease characteristics](#)

[Additional descriptions](#)

[Clinical features](#)

[Term Hierarchy](#)

[Professional guidelines](#)

[Recent clinical studies](#)

[Recent systematic reviews](#)

Genetic Testing Registry

[Deletion/duplication analysis \(188\)](#)

[Detection of homozygosity \(1\)](#)

[Detection of homozygosity \(1\)](#)

[Fluorescence in situ hybridization \(FISH\) \(1\)](#)

[Mutation scanning of select exons \(4\)](#)

[Mutation scanning of the entire coding region \(7\)](#)

[Sequence analysis of select exons \(6\)](#)

[Sequence analysis of the entire coding region \(224\)](#)

[Targeted variant analysis \(22\)](#)

[See all \(266\)](#)

Clinical resources

[OMIM](#)

[ClinicalTrials.gov](#)

Molecular resources

Practice Question #1 Using MedGen

Find a data-rich record for Alzheimer Disease. Make a note of the MedGen UID.

- What genes are associated with Alzheimer Disease?
- According to Gene Reviews, what are the causes of Alzheimer Disease?
- Are there practice guidelines for primary care providers on diagnosing Alzheimer Disease? What year were they written?
- BONUS: Does the Genetic Testing Registry include panels of genes for diagnosing Alzheimer Disease?

Practice Question #2 Using MedGen

A physician suspects that her patient doesn't respond well to clopidogrel.

- Find a MedGen record that addresses this phenomenon.
- What gene is involved in metabolizing clopidogrel?
- When were the most recent practice guidelines for clopidogrel dosing published ?
- What percentage of Chinese people are thought to be poor metabolizers of clopidogrel? *[Hint: Medical Genetics summaries link]*
- Can you find some information that may be helpful for the patient?
- BONUS: What database has detailed information on the effects of gene variants on drug response? *[Hint: It's linked from MedGen record.]*



TAKE A BREAK!

Show What You Know!

- The 1000 Genomes Project was undertaken in order to increase the _____ of the genomes represented in public databases.
- What term refers to strategies for determining what treatment is right for an INDIVIDUAL rather than what treatment is recommended for a DISEASE?
- Clinicians are not concerned about all genetic variants – only those that are _____.
- True or False? GINA (Genetic Information Nondiscrimination Act) protects you from life insurance discrimination.
- True or False? A genetic variant may originally be classified as “likely pathogenic” and later classified as “likely benign.”
- What resource would you recommend to consumers who wanted to learn more about a genetic condition?
- What is a good starting place for finding genetic information for clinicians?